REMARKS

The application has been amended to acknowledge funding.

No amendments have been made to the claims. Claims 151-156 are currently pending for examination.

Rejections under 35 U.S.C. § 112, ¶ 2

The Office Action alleges that claims 151-156 are indefinite because these claims recite that the RCG contains less than 1% of genomic material present in a whole genome and that, because this percentage appears to be a function of experimental conditions, the metes and bounds of the claim are not clear.

Initially, for clarity, it should be understood that claim 151 recites, in relevant part, "preparing a randomly primed PCR-derived reduced complexity genome (RCG) using at least one polymerase chain reaction (PCR) primer, wherein the RCG contains less than 1% of genomic material present in a whole genome," not "preparing a RCG using at least one PCR primer wherein the RCG contains less than 1% (0.05%) of genomic material present in a whole genome." Claim 151 nowhere recites 0.05% of genomic material; instead, this is recited in claim 152. It is assumed that the phrasing in the Office Action was intended to refer to both claims 151 and 152, and that this phrasing (including the deletion of several terms) was made solely in the interests of brevity in explaining this rejection, rather than as any re-interpretation of those claims. However, if this assumption is incorrect, then clarification is respectfully requested.

Regarding the interpretation of "preparing a randomly primed PCR-derived reduced complexity genome (RCG) using at least one polymerase chain reaction (PCR) primer, wherein the RCG contains less than 1% of genomic material present in a whole genome" in claim 151, the Patent Office is correct that experimental conditions are not recited in this claim. However, the fact that no experimental conditions are recited does not imply that claim 151 is indefinite.

In particular, claim 151 requires that a randomly primed PCR-derived reduced complexity genome (RCG) using at least one polymerase chain reaction (PCR) primer be prepared, and sets a requirement that the RCG that is prepared contain less than 1% of genomic material present in a whole genome. The requirement of "less than 1% of genomic material present in a whole genome"

is precisely defined. The base of the percentage is taken to be the *whole* genome, and this number will not vary *at all* based on any particular set of experimental conditions. By reciting "whole," there is no provision for only a portion of the genome to be used as the base of the percentage. Similarly, the 1% figure can be readily calculated mathematically using only the amount of genomic material within the whole genome (i.e., by just multiplying the number of nucleotides in the whole genome by 1%). Accordingly, since the claim requires that the RCG contains less than 1% of genomic material present in a whole genome, there is no room for alterations caused by any particular set of experimental conditions.

It may be helpful to consider a simple analogy here. Consider a claim that recites "preparing a piece of wood, wherein the piece of wood has a maximum length of less than 1 foot." This claim does not become indefinite just because a piece of wood could be sawed, chopped with an axe, sanded down, kicked in half, etc. until its length was less than one foot. The metes and bounds of the claim are definite and clear—this piece of wood must have a maximum length of less than one foot. The Patent Office has focused on the fact that the different techniques that could be used (e.g., sawing, chopping, sanding, kicking, etc.) have varying degrees of accuracy (e.g., it may be more difficult to aim an axe than a saw; one person may saw more accurately than another, etc.). But that does not render the claim itself indefinite. So long as that piece of wood has a maximum length of less than 1 foot, then any suitable technique may be used to prepare that piece of wood.

Accordingly, as stated in claim 151, any technique for preparing a randomly primed PCR-derived reduced complexity genome (RCG) using at least one polymerase chain reaction (PCR) primer can be used to meet the requirements of this claim step, so long as the RCG that is prepared contain less than 1% of the genomic material present in a whole genome. The metes and bounds of this claim (containing less than 1% of the genomic material present in a whole genome) are mathematically defined and clear. Thus, it is believed that this claim is not indefinite, and it is respectfully requested that this rejection be withdrawn. Claim 152 contains similar language as does claim 151 (except reciting 0.05% instead of 1%), and claims 153-156 are dependent on claims 151 or 152, and thus these claims should also be allowable for similar reasons. Withdrawal of the rejection of these claims is also respectfully requested.

Turning to the additional comments and literature citations in this rejection, the Office Action first points to portions of the specification that teach using various primers to prepare an RCG. However, the Office Action then makes an unwarranted leap that because this portion of the specification teaches using various primers to produce an RCG, this portion of the specification also teaches that this RCG must contain either less than 1% or less than 0.05% of genomic material present in a whole genome.

The portion of the specification identified in the Office Action merely teaches that various RCGs can be prepared using various primers, and does not place any restrictions on the size of the RCG that is prepared. Accordingly, it is not seen how the Patent Office can conclude, based on this portion of the specification, that the resulting RCGs must contain either less than 1% or less than 0.05% of genomic material present in a whole genome. In fact, elsewhere in the specification, RCGs having a variety of sizes are discussed. See, e.g., page 18, lines 12-19.

The Office Action also appears to suggest that the specification must provide a calculation in order to determine which prepared RCGs would represent less than 1% or less than 0.05% of the genome. It should be noted that the specification teaches various techniques for using a PCR primer to prepare an RCG, such as IRS-PCR, AP-PCR, DOP-PCR, multiple primed PCR, adaptor-PCR, etc., and the specification teaches that the length and complexity of an RCG that is prepared can be controlled by controlling by selecting DOP-PCR primers having shorter or longer TARGET and $(N)_x$ nucleotide sequences. See, e.g., page 18, line 32 to page 19, line 23, or page 20, line 28 to page 22, line 7. As noted in the Office Action, the number of nucleotides in a primer such as a tag-$(N)_x$-TARGET primer is not large; thus, optimizing a given PCR technique to prepare an RCG using PCR primers such that the RCG contains less than 1% (or 0.05%) of genomic material present in a whole genome is not difficult and does not require undue experimentation, although the exact size of the RCG may vary somewhat based on the technique used, as the Office Action notes. However, as is discussed in the instant specification, a person of ordinary skill in the art would be able to routinely prepare RCGs using any PCR technique that is well-known, determine the length of the prepared RCGs, and compare that length to the whole genome to determine whether or not the length of the prepared RCGs is less than 1% (or 0.05%) of the whole genome, without any undue experimentation.

Regarding Cheung, *et al.*, *Proc. Natl. Acad. Sci. USA*, 93:14676-14679, 1996 ("Cheung"), the Patent Office appears to be arguing that Cheung is inconsistent with itself. Applicants were not involved with the Cheung study and thus cannot vouch for its accuracy. However, it would appear that, since the Patent Office's estimates use numbers with only *one* significant digit (e.g., 3×10^9 base pairs in a human genome), to conclude that 10% is "vastly different" from 16% based on a rough calculation involving only a single significant digit would appear to be a gross oversimplification.

Regarding Fisher, *et al.*, *Nucleic Acids Research*, 24(21):4369-5371, 1996 ("Fisher"), the Patent Office states that the amplicons prepared in Fisher are dependent on PCR amplification conditions. However, the Patent Office has assumed, without any evidence, that amplicons are equivalent to an RCG, and further, as noted above, while Fisher has demonstrated that some variability may occur, it is not seen how that variability renders indefinite the requirement in claim 151 that the RCG contains less than 1% of genomic material present in a whole genome. One of ordinary skill in the art simply needs to measure the amount of RCG prepared using the Fisher technique, and determine whether that amount is greater or less than 1% of genomic material present in a whole genome.

Osman, *et al.*, *Plant Physiology*, 131:1294-1301, 2003 ("Osman") appears to be cited to demonstrate that, by using different primers, different amounts of PCR products may be prepared. Again, the issue is not whether Osman's technique produces different amounts of PCR products using different primers, but whether one of ordinary skill in the art would be able to determine whether a particular RCG prepared using any of Osman's techniques contains less or more than 1% of genomic material present in a whole genome.

Accordingly, although the Patent Office is correct that using different primers under varying experimental conditions may potentially result in different amounts of RCG being prepared, it does not follow that any of claims 151-156 are unclear or indefinite. A person of ordinary skill in the art need only to be able to determine the amount of RCG present, as prepared using a PCR primer as is recited in claim 151 (using any suitable technique), and determine whether that RCG contains more or less than 1% of genomic material present in a whole genome. Accordingly, it is respectfully requested that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a) in view of Shuber, Wei, Saiki, and Von Eggeling

Claims 151-153, 155, and 156 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Shuber, *et al.*, U.S. Pat. No. 5,589,330 ("Shuber") in view of Wei, *et al., Somatic Cell and Molecular Genetics*, 20(5):401-408, 1994 ("Wei") and Saiki, *et al.*, Int. Pat. Apl. Pub. No. WO 89/11548 ("Saiki") as evidenced by Von Eggeling, *et al.*, *Cellular and Molecular Biol*ogy, 41(5):653-570, 1995 ("Von Eggeling").

This rejection was made based upon the alleged indefiniteness of the determination of the percentage of RCG, as was noted in the Office Action (see, e.g., page 7). In particular, the Patent Office has interpreted the teaching in the specification that a degenerate primer with at least 8 nucleotide specificity can be used to prepare an RCG to mean that a degenerate primer with at least 8 nucleotide specificity would result in an RCG of less than 1% or less than 0.05%.

As discussed above, however, there is no ambiguity in determining the amount of genomic material in an RCG and comparing that to the amount within the whole genome, and the specification does not inherently teach that a degenerate primer with at least 8 nucleotide specificity produces an RCG of less than 1% or less than 0.05%. Consequently, the premises that this rejection is based on are invalid. Thus, it is respectfully requested that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a) in view of Shuber, Guilfoye, and Saiki

Claims 151, 152, and 154-156 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Shuber in view of Guilfoye, *et al., Nucleic Acids Research*,25(9):1854-1858 ("Guilfoye") and Saiki.

This rejection is also based upon the alleged indefiniteness of the determination of the percentage of RCG, as was noted on page 12 of the Office Action. The same assumptions discussed above with respect to Shuber, Wei, Saiki, and Von Eggeling were also applied to this rejection. Thus, for at least the reasons discussed above (i.e., that there is no ambiguity in determining the amount of genomic material in an RCG and comparing that to the amount within the whole genome, and the specification does not inherently teach that a degenerate primer with at least 8 nucleotide

specificity produces an RCG of less than 1% or less than 0.05%), the premises of this rejection are invalid. Accordingly, it is respectfully requested that this rejection be withdrawn.

CONCLUSION

Favorable action is respectfully requested. If, for any reason, the Examiner is of the opinion that a telephone conversation with the Applicants' representative would expedite prosecution, the Examiner is kindly invited to contact the undersigned at the number below.

No fee is believed due with this response. However, if a fee is due, including an extension fee, please charge Deposit Account No. 23/2825 under Docket No. M0656.70098US00, from which the undersigned is authorized to draw.

Dated: October 27, 2011

Respectfully submitted,

By /Tani Chen/

Tani Chen, Sc.D.
Registration No.: 52,728
Helen C. Lockhart, Ph.D.
Registration No.: 39,248
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000